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CLINICAL RESEARCH

Association between resting heart rate and arterial stiffness in Korean adults

Association entre le rythme cardiaque au repos et la rigidité artérielle chez les adultes coréens

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KEYWORDS

Heart rate;
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Pulse wave velocity

Summary

Background. — Higher resting heart rate, a simple and useful indicator of autonomic balance and metabolic rate, has emerged as an independent predictor for atherosclerotic cardiovascular disease.

Aim. — To determine the association between resting heart rate and arterial stiffness measured by brachial-ankle pulse wave velocity (baPWV).

Methods. — We examined the association between resting heart rate and baPWV in 641 Korean adults (366 men, 275 women) in a health examination program. A high baPWV was defined as greater than 1450 cm/s (> 75th percentile). The odds ratios for high baPWVs were calculated using multivariable logistic regression analysis after adjusting for confounding variables across heart rate quartiles (Q1 ≤ 56, Q2 = 57–62, Q3 = 63–68, Q4 ≥ 69 beats/min).

Results. — Age-adjusted baPWV mean values increased gradually with heart rate quartile (Q1 = 1281, Q2 = 1285, Q3 = 1354, Q4 = 1416 cm/s). The odds ratios (95% confidence intervals) for high baPWVs in each heart rate quartile were 1.00, 1.28 (0.57–2.86), 2.63 (1.20–5.79) and 3.66 (1.66–8.05), respectively, after adjusting for age, sex, smoking status, alcohol intake, exercise, body mass index, hypertension medication, diabetes medication, hyperlipidaemia medication, mean arterial blood pressure, fasting plasma glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, white blood cell count, aspartate aminotransferase, alanine aminotransferase, γ -glutamyltransferase and uric acid.

Abbreviations: baPWV, brachial-ankle pulse wave velocity; CI, confidence interval; HDL, high-density lipoprotein; HR, heart rate; PWV, pulse wave velocity; WBC, white blood cell.

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MOTS CLÉS

Rythme cardiaque ;
Maladie
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Rigidité artérielle ;
Vitesse de l'onde de
pouls

Conclusion. — These findings indicate that a higher resting heart rate is independently associated with arterial stiffness. Accordingly, early detection of increased resting heart rate is important for preservation of arterial function and assessment of cardiovascular risk.

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Résumé

Le contexte. — Un rythme cardiaque plus élevé au repos, un indicateur simple et utile de l'équilibre autonome et du métabolisme, est apparu comme un indicateur de maladie cardiovasculaire athérosclérotique.

Objectif. — Déterminer l'association du rythme cardiaque élevé au repos avec la rigidité artérielle par la vitesse de l'onde de pouls cheville/bras (*brachial-ankle pulse wave velocity* [baPWV]).

Méthode. — Nous examinons l'association entre le rythme cardiaque élevé au repos et le baPWV sur 641 adultes coréens (366 hommes, 275 femmes) dans le cadre du programme de l'examen. Un baPWV élevé est défini lorsque celui-ci dépasse plus de 1450 cm/s (> 75^e percentile). L'*odds ratio* (ou rapport de chances) pour le baPWV élevé a été calculé en utilisant l'analyse de la régression logistique multivariée, après rectification des variables de perturbation à travers les quartiles du rythme cardiaque élevé au repos (Q1 ≤ 56, Q2 = 57–62, Q3 = 63–68 et Q4 ≥ 69 battements par minute).

Résultats. — Le baPWV à l'âge ajusté signifie que les valeurs ont progressivement augmenté avec le quartile du rythme cardiaque élevé au repos (Q1 = 1281, Q2 = 1285, Q3 = 1354 et Q4 = 1416 cm/s). L'*odds ratio* (95 % CI) pour le baPWV élevé dans chaque quartile du rythme cardiaque élevé au repos était 1,00 ; 1,28 (0,57–2,86) ; 2,63 (1,20–5,79) et 3,66 (1,66–8,05), après l'ajustement de l'âge, du sexe, du tabagisme, de la consommation d'alcool, de l'exercice physique, de l'indice de masse corporelle, de la prise de médicament contre l'hypertension, de la pression artérielle moyenne, de la mesure de la concentration du glucose, du cholestérol total, des triglycérides, du HDL-cholestérol, du nombre de leucocytes, de l'aspartate aminotransférase, de l'alanine aminotransférase, de la gamma glutamyl transférase et de l'acide urique.

Conclusion. — Ces découvertes indiquent qu'un rythme cardiaque plus élevé au repos est indépendamment associé avec la rigidité artérielle. En conséquence, un dépistage rapide d'un rythme cardiaque plus élevé au repos est important pour la préservation de la fonction artérielle et l'évaluation du risque cardiovasculaire.

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Background

Resting heart rate (HR) is a simple and useful indicator of autonomic balance and metabolic rate [1]. Emerging evidence has shown that higher resting HR is linked closely to all-cause and cardiovascular disease mortality [2–4], but the mechanism remains unclear. Higher HR may be associated with oxidative stress and chronic subclinical inflammation because of the increased rate of oxygen consumption [5–7]. Chronic low-grade arterial inflammation is known to be associated with the pathogenesis of cardiovascular disease [8,9]. Several studies have reported that various inflammatory markers, such as high-sensitivity C-reactive protein, erythrocyte sedimentation rate, and white blood cell (WBC) count, are associated with arterial stiffness [10,11].

Increased arterial stiffness as measured by pulse wave velocity (PWV) has been reported to be a significant predictor of cardiovascular events and mortality [12,13]. Recently, a simple, automated device has become available for the measurement of brachial-ankle pulse wave velocity (baPWV), using a volume-rendering method. Measuring baPWV is easier and more efficient than conventional measurements of aortic PWV and also has a good correlation

with aortic PWV [14]. Moreover, a previous study assessed and confirmed the validity, reliability and reproducibility of this measurement [15].

If the link between resting HR and cardiovascular disease morbidity and mortality is indeed mediated by chronic low-grade arterial inflammation, we would expect positive associations between resting HR and arterial stiffness. Therefore, we examined the associations of resting HR with arterial stiffness in Korean adults, as measured by baPWV.

Methods**Study population**

We reviewed the medical records of 728 participants (416 men, 312 women) who underwent a medical examination at the health promotion centre in Gangnam Severance Hospital, Yonsei University College of Medicine between March 2006 and May 2007. Subjects meeting any of the following criteria were excluded ($n=87$): any missing covariate information and ankle brachial index less than 0.9; a history of arrhythmia or thyroid disease; a history of coronary heart disease or stroke. After exclusions, 641 participants

(366 men, 275 women) were included in the final analysis. This study was approved by the Institutional Review Board of Yonsei University College of Medicine and informed consent was obtained from each participant. The examinations were performed by medical staff according to standard procedures. Participants were asked about lifestyle behaviour, including cigarette smoking, alcohol consumption and physical activity (more or less than two times per week), as well as whether they were currently undergoing treatments for any disease. If so, they were asked for the date of diagnosis and a list of current medications. Trained staff reviewed the completed questionnaires and entered the responses into a database. Participants were classified as non-smokers, ex-smokers or current smokers. They were also classified in terms of alcohol intake as non-drinkers or current drinkers. Body mass index was calculated as weight divided by height squared (kg/m^2).

After a 12-hour overnight fast, blood samples were taken from an antecubital vein. WBC counts were quantified by an automated blood cell counter (ADVIA 120, Bayer, NY, USA). Fasting plasma glucose, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, aspartate aminotransferase, alanine aminotransferase, γ -glutamyltransferase and uric acid were measured using a Hitachi 7600-110 Chemistry Autoanalyzer (Hitachi, Tokyo, Japan). Diabetes was defined as a self-reported history of the disorder or a fasting plasma glucose level greater or equal to 7.0 mmol/L . Hypertension was defined as a self-reported history of the disorder, systolic blood pressure greater or equal to 140 mmHg or diastolic blood pressure greater or equal to 90 mmHg .

Definition of metabolic syndrome

The modified National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) was used for the definition of metabolic syndrome [16]. Metabolic syndrome was defined by the presence of three or more of the following risk factors: waist circumference greater or equal to 90 cm for men and greater or equal to 80 cm for women [17]; high triglyceride concentration ($\geq 150 \text{ mg/dL}$); low HDL-cholesterol concentration ($< 40 \text{ mg/dL}$ for men and $< 50 \text{ mg/dL}$ for women); elevated systolic blood pressure ($\geq 130 \text{ mmHg}$) or elevated diastolic blood pressure ($\geq 85 \text{ mmHg}$); high fasting plasma glucose concentration ($\geq 100 \text{ mg/dL}$), based on the revised American Diabetes Association criteria [18]. Subjects who reported taking anti-hypertensive or antidiabetic medications were considered to have elevated blood pressure or high fasting plasma glucose.

Brachial-ankle pulse wave velocity measurement

An automatic waveform analyzer (model BP-203RPE; Colin Co., Komaki, Japan) was used to measure PWV. This instrument simultaneously records venous blood pressure, phonocardiogram, electrocardiogram and arterial blood pressure at both brachial arteries and ankles. Participants were examined in the supine position after 10 minutes of bed rest. Electrocardiogram electrodes were placed on both wrists and a microphone for the phonogram was placed on the left edge of the sternum. Pneumonic cuffs were

wrapped around both upper arms and ankles and connected to a plethysmographic sensor to determine the volume pulse waveform. Waveforms for the upper arm (brachial artery) and ankle (tibial artery) were stored for 10-s sample times with automatic gain analysis and quality adjustment. Oscillometric pressure sensors were attached to the cuffs to measure blood pressure in the four extremities. The baPWVs were recorded using a semiconductor pressure sensor (1200 Hz sample acquisition frequency) and calculated using the following equation:

$$(La - Lb) / \Delta Tba$$

La and Lb were defined as the distance from the aortic valve to the elbow and to the ankle, respectively. The distance from the suprasternal notch to the elbow (La) and from the suprasternal notch to the ankle (Lb) were expressed by:

$$La = 0.2195 \times \text{height of participant (cm)} - 2.0734 \text{ and}$$

$$Lb = 0.8129 \times \text{height of participant (cm)} + 12.328$$

The time interval between the arm and ankle distance (ΔTba) was defined as the pulse transit time between the brachial and tibial arterial pressure waveforms. La and Lb were estimated automatically based on the participants' heights.

Statistical analysis

HR quartiles were categorized as follows: $Q1 \leq 56$, $Q2 = 57-62$, $Q3 = 63-68$, and $Q4 \geq 69 \text{ beats/min}$. Demographic and biochemical characteristics of the study population according to HR quartiles were compared using one-way analysis of variance for continuous variables and the chi-squared test for categorical variables. Age-adjusted baPWV means and standard errors were calculated using analysis of covariance according to HR quartiles. Individuals were divided into two groups based on baPWV: the high group ($> 75\text{th percentile}$) and the low group ($\leq 75\text{th percentile}$). Therefore, a high baPWV was defined as greater than 1450 cm/s . The odds ratios for high baPWVs were calculated using a multivariable logistic regression analysis after adjusting for confounding variables across HR quartiles. All analyses were conducted using SAS statistical software, version 9.1 (SAS Institute Inc, Cary, NC, USA). All statistical tests were two-sided, and statistical significance was determined at a P -value less than 0.05.

Results

The study population characteristics according to HR quartiles are shown in Table 1. Systolic blood pressure, diastolic blood pressure, fasting plasma glucose, uric acid and WBC counts were highest in Q4. The prevalence of metabolic syndrome increased in accordance with HR quartiles.

Fig. 1 shows the age-adjusted means and standard errors of baPWV (cm/s) according to HR quartiles. The age-adjusted means increased gradually according to HR

Table 1 Clinical and chemical characteristics of the study population according to heart rate quartile.

	Heart rate quartiles				<i>P</i> -value
	Q1 (≤ 56 beats/min) ^a (<i>n</i> = 131)	Q2 (57–62 beats/min) ^a (<i>n</i> = 174)	Q3 (63–68 beats/min) ^a (<i>n</i> = 177)	Q4 (≥ 69 beats/min) ^a (<i>n</i> = 159)	
Age (years)	50.7 (11.6)	48.3 (11.7)	46.9 (11.6)	47.0 (11.7)	0.023
Women	32.8	47.1	46.9	42.1	0.048
Body mass index (kg/m ²)	23.9 (2.5)	23.5 (3.0)	23.9 (2.8)	23.9 (3.1)	0.597
Current smoker	22.9	17.8	20.3	22.0	0.127
Alcohol ingestion ^b	71.7	69.5	75.1	66.6	0.373
Regular exercise ^c	51.1	58.6	64.9	56.6	0.102
Systolic blood pressure (mmHg)	119.6 (15.4)	117.4 (16.0)	119.2 (14.8)	123.2 (14.3)	0.005
Diastolic blood pressure (mmHg)	73.0 (11.5)	70.9 (12.2)	73.4 (11.2)	75.9 (12.2)	0.002
Fasting plasma glucose (mmol/L)	5.3 (0.8)	5.2 (0.7)	5.4 (1.2)	5.6 (1.5)	0.008
Total cholesterol (mmol/L)	5.1 (0.9)	4.9 (0.9)	5.0 (0.9)	5.0 (0.9)	0.383
HDL-cholesterol (mmol/L)	1.2 (0.3)	1.3 (0.3)	1.2 (0.3)	1.2 (0.3)	0.514
Triglyceride (mmol/L)	1.2 (0.7)	1.2 (1.0)	1.3 (1.3)	1.4 (1.0)	0.137
WBC count ($\times 10^9$ cells/L)	5.3 (1.2)	5.3 (1.3)	5.6 (1.5)	5.8 (1.3)	0.001
Hypertension ^d	23.5	20.1	20.9	28.9	0.222
Diabetes ^e	4.6	3.5	3.4	8.2	0.143
Metabolic syndrome	22.1	23.0	30.5	32.7	0.084

Data are expressed as mean (standard deviation) or percentage.

HDL-cholesterol: high-density lipoprotein cholesterol; WBC: white blood cell.

^a Resting heart rate.

^b Alcohol drinking ≥ 20 g/day.

^c Regular exercise \geq once/week.

^d Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or a history of the disorder.

^e Diabetes was defined as fasting plasma glucose concentration ≥ 7.0 mmol/L, or a history of the disorder.

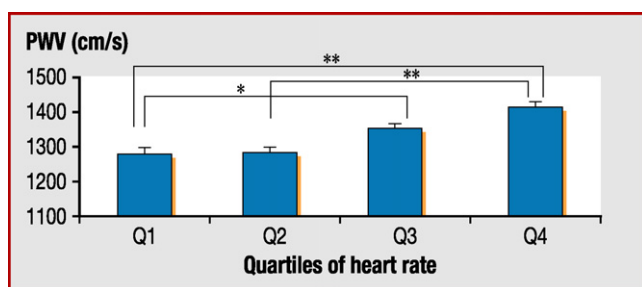


Figure 1. Age-adjusted means of brachial-ankle pulse wave velocity according to heart rate quartile. Bars represent standard errors. * $P < 0.01$. ** $P < 0.05$. PWV: pulse wave velocity.

Table 2 Correlation between brachial-ankle pulse wave velocity and other indicators of cardiovascular risk.

Variables	r^a	P -value ^b
Age	0.624	< 0.001
Heart rate	0.159	< 0.001
White blood cell count	0.200	< 0.001
Framingham risk score	0.470	< 0.001
Metabolic syndrome	0.373	< 0.001

^a Correlation coefficient.

^b P -value by Pearson's correlation analysis.

quartiles: Q1 = 1281 (17.1), Q2 = 1285 (14.8), Q3 = 1354 (14.7), and Q4 = 1416 (15.5) cm/s.

Table 2 shows the correlation between baPWV and other indicators for cardiovascular risk. BaPWV was significantly correlated with age, HR, WBC count, Framingham risk score and metabolic syndrome.

Table 3 shows the risk for high baPWV according to HR quartiles. In multiple logistic regression model 1, the odds ratios (95% confidence intervals [CIs]) for high baPWVs across the HR quartiles were 1.00, 1.10 (0.57–2.14), 2.65 (1.39–5.04) and 4.74 (2.47–9.09), respectively, after adjusting for age and sex. We also assessed the association between HR and the risk for high baPWV after additional adjustment for cigarette smoking, alcohol intake, regular exercise, body mass index, hypertension

medication, diabetes medication, hyperlipidaemia medication, mean blood pressure, fasting plasma glucose, total cholesterol, triglycerides, HDL-cholesterol, WBC count, aspartate aminotransferase, alanine aminotransferase, γ -glutamyltransferase and uric acid. The associations were similar after using models 2 and 3 (Table 3). The multivariable adjusted odds ratios (95% CI) for the highest versus the lowest quartile of HR were 4.58 (2.38–8.83) and 3.66 (1.66–8.05), respectively, in model 2 and model 3.

Discussion

In this cross-sectional study, we found a positive association between resting HR and baPWV, independent of classic cardiovascular risk factors. This association remained after adjusting for other potential risk and confounding factors. A high baPWV was defined as greater than 1450 cm/s in our study. This cut-off value can be used as a surrogate marker for increased arterial stiffness because a baPWV greater than 1400 cm/s has been shown to be a useful predictor of cardiovascular disease [19]. Moreover, our study showed that baPWV was significantly correlated with Framingham risk score.

Arterial stiffness is caused by structural and functional changes within the arterial walls, resulting in an increased PWV. Some mechanisms could explain the significant relationship between resting HR and arterial stiffness. Firstly, because resting HR can reflect an autonomic balance, a higher HR may indicate a higher ratio of sympathetic/parasympathetic activity [20], which can lead to increased vascular tone and resistance [21]. Increased sympathetic tone is positively correlated with a higher rate of oxygen consumption and increased production of proinflammatory cytokines, such as interleukin-6 and tumour necrosis factor- α [22,23]. These cytokines play a key role in regulating vessel wall tone by affecting the release of nitric oxide and endothelin-1 in the subendothelial space [24,25]. This cascade may cause endothelial dysfunction and alter arterial elastic properties, leading to structural stiffness. Mayer et al. reported that beta-adrenergic blocker treatment attenuated resting HR and interleukin-6 simultaneously in heart failure patients under higher sympathetic tone status [26]. Additionally, Borovikova et al. showed

Table 3 Odds ratios and 95% confidence intervals for a high brachial-ankle pulse wave velocity, according to heart rate quartiles.

	Heart rate quartiles				P for trend
	Q1	Q2	Q3	Q4	
Model 1 ^a	1.00	1.11 (0.57–2.14)	2.65 (1.39–5.04)	4.74 (2.47–9.09)	< 0.001
Model 2 ^b	1.00	1.06 (0.54–2.05)	2.60 (1.36–4.97)	4.58 (2.38–8.83)	< 0.001
Model 3 ^c	1.00	1.28 (0.57–2.86)	2.63 (1.20–5.79)	3.66 (1.66–8.05)	< 0.001

^a Adjusted for age and sex.

^b Adjusted for age, sex, smoking status, alcohol intake, regular exercise and body mass index.

^c Adjusted for age, sex, smoking status, alcohol intake, regular exercise, body mass index, hypertension medication, diabetes medication, hyperlipidaemia medication, mean arterial blood pressure, fasting plasma glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, white blood cell count, aspartate aminotransferase, alanine aminotransferase, γ -glutamyltransferase and uric acid.

that vagal nerve stimulation reduced biomarkers of systemic inflammation [27]. Secondly, a higher HR may also reflect an increased metabolic rate, leading to increased oxidative stress and chronic low-grade inflammation. WBC count is a usual marker of systemic inflammation, and it was highest in the fourth HR quartile of the present study. WBC count is a useful predictor of coronary artery disease, stroke, peripheral artery disease, carotid atherosclerosis, hypertension and diabetes [21,28,29]. The significant associations between resting HR and WBC count in the present study also support the concept that resting HR may be involved in oxidative stress and systemic inflammation. Moreover, we documented that an elevated WBC count was associated with arterial stiffness in a previous study [11]. Therefore, resting HR and arterial stiffness may be linked by a chronic, low-grade inflammation in the vessel walls. In an animal study, induced tachycardia has been proposed to elevate the level of cardiac nicotinamide adenine dinucleotide and mitogen-activated protein kinase, indicators of oxidative stress to heart [7].

Our study showed the similar patterns of association between resting HR and baPWV after adjusting for the presence of drugs that could modify both HR and PWV, such as blood pressure-lowering drugs, antidiabetic drugs, and lipid-lowering drugs. Until now, no human studies have been performed to show the benefit of HR-slowness measures in participants without heart disease. However, recent epidemiological studies in patients with heart disease have reported that HR slowing improves prognosis, whereas increased HR has detrimental effects on survival [30,31]. Therefore, resting HR may have its own effects on cardiovascular properties that are independent of HR-altering manoeuvres.

Our study had several limitations. Firstly, it was a cross-sectional design, which suggests that caution should be used in causal interpretations. Interestingly, acute faster HR induced by a pacemaker may increase PWV in humans [32]. However, this result does not represent a structural change but rather a functional one within individuals. Our study focused on chronic intrinsic properties of HR in individuals rather than the functional effects resulting from temporal HR change. Secondly, only one resting HR measurement was included in the analysis. However, it is important to note that although ambulatory HR varies from hour to hour according to activity, resting HR is stable and represents basal metabolic rate and autonomic activity for a long period of time.

Conclusion

Our findings demonstrate that a higher resting HR is independently associated with arterial stiffness. Accordingly, early detection of increased resting HR is important in the assessment of potential cardiovascular risk and could be an initiative for HR slowing and the prevention of cardiovascular disease.

Conflict of interest statement

None.

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